DESIGN, FORMULATION AND EVALUATION OF BILAYER TABLET OF ETORICOXIB AND THIOCOLCHICOSIDE: A CHRONOMODULATED APPRAOACH

SYNOPSIS OF THE THESIS

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DECLARATION

I hereby declare that the dissertation synopsis entitled **"Design, Formulation and Evaluation of Bilayer Tablet of Etoricoxib and Thiocolchicoside: A Chronomodulated Approach "** to be submitted for partial fulfillment of degree of Doctor of Philosophy is my original work and the dissertation has not formed the basis for the award of any degree, diploma, associateship or fellowship of similar other titles. It has not been submitted to any other University or Institution for the award of any degree or diploma.

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INTRODUCTION:

The cost and difficulties involved in marketing new drug product has been increased over the past 30 years, with concomitant identification of pharmacological or therapeutic advantage of control drug delivery. Recently the most frequently used technique for treating the disease or illness is chemotherapy. [1] The drugs used in combination for treatment of diseases has advantages over monotherapy as side effects are minimized and also low dose combination of two different drugs minimizes dose related risk. [2]. In the present era various developing and developed countries are moving towards combination therapy for the treatment of different types of diseases such as hypertension, diabetes, gout etc. The aim of preparing the bilayer tablet or control release tablet is to minimize the dosing frequency. The design of modified release is to optimize and maximize the pharmacological effectiveness by providing the slow and continuous delivery of drug over entire dosing interval providing greater patient compliance and convenience. Coronary vasodialators, antihypertensive, antihistamines, analgeics, antipyratics, antigout, antidiabitic categories are mainly suitable for bilayer tablet formulation. [3]

Advantages of Bilayer Tablet: [4]

1. Cost effective as compared to other conventional dosage form.

2. The drugs or excipients which cause incompatibility can be separated into different individual layers in single tablet.

3. Product can be recognized easily.

4. Daily dose requirement is less in comparison to traditional delivery system.

5. Packaging and shipment is easy. [1]

6. Bilayer tablet has better physical and chemical stability. [1]

Disadvantages of Bilayer tablet: [4]

1. Children and unconscious patient cannot swallow tablet easily.

2. Bilayer tablet has some untoward problems such as insufficient hardness, layer saperation and reduced yield.

3. Weight control of individual layer is not accurate.

4. Some drugs having amorphous nature and low density character retard compression into dense compact.

Types of Bilayer Tablet: [1]

Bilayer tablets are of two types:

1. Homogeneous Type: These are preferred when release profile of drugs are different from each other. Bilayer tablet is used when one layer of drug or tablet is formulated or designed as immediate release and second layer of drug or tablet is designed into sustained release.

2. Heterogeneous Type: These are prepared to separate two incompatible substances and are used for sequential release of two drugs in combination.

Technologies Used For Preparation of Bilayer Tablet: [5]

1. OROS PUSH PULL TECHNOLOGY: This technology contains two or three layers mainly in which one or more layer contains drug and either layer is push layer. The drug layer contains drug and two or more ingredients. So this drug layer contains drug having poor solubility. Further osmotic agents and suspending agents are added. Semi permeable membrane helps in surrounding the tablet core.

2. OROS TM TECHNOLOGY: This technique is used to resolve the solubility criteria. The L-OROS system is developed by Alza in which drug containing liquid soft gel product in dissolved state is initially manufactured and then coating is done with a barrier membrane, then by osmotic layer and semi permeable membrane which is drilled with an exit orifice.

3. EN SO TROL TECHNOLOGY: This technique is used for the solubility enhancement or for the formulation of optimized dosage form. In this technique Shire laboratory used an integrated approach to delivery of drugs which generally focus on identification and incorporation of identified enhancer into control release technologies.

4. DUROS TECHNOLOGY: In this system outer cylindrical reservoir is present. The reservoir contains impact strength and so it protects the drug molecule from enzymes.

Solubility Enhancement: The techniques used for solubility enhancement are solid dispersion, complexation, microwave assisted technique, co solvency, pH adjustment, particle size reduction, micoemulsion, micellar solubilization, supercritical fluid extraction etc. [6]

1. Complexation: Cyclodextrin is used as a complex to enhance the solubility and drug stability. Cyclodextrin for pharmaceutical use contain 6, 7 and 8 molecules. B cyclodextrin generally increase water solubility are most commonly used in pharmaceutical formulations.

2. Solid Dispersion: It is used to enhance the solubility of poorly soluble drug. In this method poorly soluble drug is dispersed in highly soluble dispersed matrix which increases the dissolution rate of the drug. [6]

Types of solid dispersion:

Binary Solid Dispersion: It consists of drug and a polymer carrier.

Ternary Solid Dispersion: It consists of drug, a polymer carrier and a surfactant. [7]

3. Cosolvency: The solubility of poorly soluble drug can be increased by addition of cosolvent in which drug has good aqueous solubility. It generally contains mixture of water and water miscible solvents. It is most commonly used technique to increase and evaluate the solubility. [6]

4. Lyophillization: It is also used to enhance the solubility of poorly aqueous soluble drug. It works on the principle of triple point. This technique is also called as sublimation technique.

Optimization: The word optimize means to make perfective and effective as much as possible. It is required for designing the schemes and formulas and thus makes the successful formulations. Various terms that used in optimization are variable, factor, level, response etc. [8]

Software for designs and optimization: Many commercial software packages are available which are either dedicated to experimental design alone or are of a more general statistical type. Software's dedicated to experimental designs

Design Expert

Echip Multi-Simplex

Nemrodw

Software for general statistical nature

Sas

Minitab

Systat

Graphpad

Prism

Pharmacokinetic Model Study:

It refers to drug release kinetics study. The drug release kinetics is estimated by the release from the sustained layer and the data of invitro drug release is fitted into different models. The technique is used using PCP Disso software developed by Poona College of Pharmacy, India for zero order, first order, Higuchi, Hixson–Crowell, Korsmeyer–Peppas, models with ANOVA treatment for the dissolution data. [9]

Pharmacodynamic model study:

Rat models are used to carry Antigout activity. For Antigout Study of the considered drug 30 rats will be taken in five groups, each group consist of 6 rats. **GROUP 1** will act as vehicle control group, **GROUP 2** is used as gout control group, **GROUP 3** will be used as standard treatment control group, **GROUP 4** will be used as treatment group, **GROUP 5** will be used as standard treatment control group and treatment group. At the end of study blood collection

is performed and it is studied for heamatological parameters and biochemical parameters. Further statistical analysis will be carried out by one way ANOVA [10]

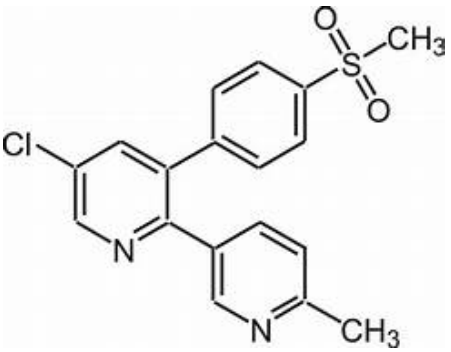
Stability Study: The accelerated stability study of optimized formulation is carried for three months and evaluated for various parameters such as appearance, friability, hardness, thickness, disintegration time, dissolution time.

Drug Profile:

1. Etoricoxib

IUPAC Name: 5-Chloro-6-methyl-3-[4-(methylsulfonyl)phenyl]-2,3-bispyridine

Structure:



Empirical Formula: $C_{18}H_{15}ClN_2O_2S$

Category: Post arthritis, psoriatic arthritis, osteoarthritis, ankylosing spomdylitis, chronic low back pain, acute pain and gout.

Color: White

Molecular Weight: 358.84gmol^{-1}

BCS Class: BCS Class II

pKa – 4.5

Half Life: 22 hours

Bioavailability- 100%

Melting Point - 127°C - 128°C

Solubility: Poor solubility in water and other solvents

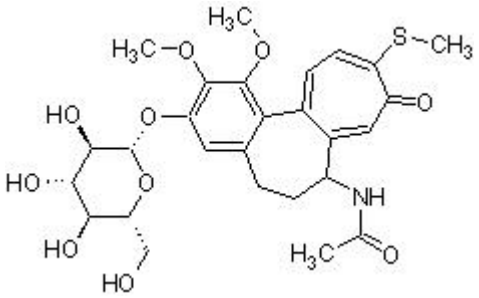
Metabolism: Hepatic, CYP extensively involved

Mechanism of Action: Etoricoxib effectively inhibits isoform 2 of enzyme cyclooxegenase i.e COX 2. It has approximately 106 fold selectivity for COX 2 inhibition over COX 1. This diminishes the generation of prostaglandin and arachidonic acid.

2. Thiocolchicoside:

IUPAC Name: N-[(7S)-3-(β-D-Glucophranasloxy)-1,2-dimethoxy-10-methoxy-10-(methylsulfony)-9-oxo-5,6,7,9-tetrahydrobenzo [a] heptan-7-yl]ethanamide

Structure:



Empirical Formula: $C_{27}H_{33}NO_{10}S$

Category: It is used as muscle relaxant with anti-inflammatory and analgesic effect

Molecular Weight: 563.618g/mol

Elimination Half Life: 5-6 Hours

Bioavailability: 25%

Melting Point: 190°C -198°C

pKa: 12.74

Solubility: Soluble in water and alcohol

BCS Class: BCS Class III

Density: 1.222

Refractive Index: 1.6550

Mechanism of Action: It acts as GABA receptor antagonist and also glycine receptor antagonist with similar potency and nicotinic acetylcholine receptor to much less extant. It is a synthetic sulfur derivative of colchisidase a naturally occurring glycoside contained in colchicum autumnale plant. Thiocolchicoside have selective and potent affinity for GABA-A receptor and act as muscle contraction by activating the GABA inhibitory pathways thereby behaving as a potent muscle relaxant. The major inhibitory neurotransmitter in human cortex is GABA.

AIM AND OBJECTIVE:

The present invention relates to the formulation and development of bilayer tablet having immediate release layer and a sustained release layer with immediate release layer containing Etoricoxib and sustained release layer containing Thiocolchicoside. The tablet of present invention features a balance between immediate release of Etoricoxib and sustained release of Thiocolchicoside, which provides a significantly more uniform, efficient delivery of both the antigout drugs as compared to other marketed formulation currently available. This dosage form may be used in same indication as individual tablet of Thiocolchicoside and Etoricoxib now in clinical use. However it is especially useful where it is desirable to maintain a sustained uniform dose of drugs for twelve to twenty-four hours with the administration of only one dose as well as with an immediate effect.

In particular the solid dosage form of present invention may be in the form of compressed bilayer tablet containing having at least one layer containing Etoricoxib immediate release and another layer containing thiocolchicoside formulated as sustained release.

RATIONALE AND SCOPE OF THE STUDY:

Bilayer tablet has gained immense attention due to their ability to deliver the drug at right site of action, in right amount and in right time. They are designed as per body's circadian rhythm. Numerous disease such as angina pectoris, ulcer, rheumatoid arthritis, hypertension, myocardial infraction and bronchial asthma show circadian variations in their onset and symptoms exacerbation. To combat this problem a dosage form with modified drug release profile having one immediate release layer and other sustained release layer that releases the drug after a lag time is advantageous.

Gout is arthritis that happens when you have too much uric acid in blood and it forms sharp crystal in one of your joints. Big toe is most common place for it to happen; symptoms are sudden and severe pain in joint usually in middle of night and early morning. Acute gout attack occurs two times more during night and early morning than during day. There is a risk among patient with low purine intake in 24 hours prior to attack. When breaking down purine body produces uric acid. Certain foods are high in purine including organ meat, sea food and alcohol. The measures that prevent gout flares especially at night may be more effective. Thus an ideal drug delivery in this case will be to administer the drug at bed time, but drug release would take place from midnight, through early hour in morning and then during the day.

In the present work, development and evaluation of bilayer tablet formulation using different polymers have been attempted to treat arthritis and gout. Etoricoxib and Thiocolchicoside have proved to be effective in preventing gout and arthritis. There aimed to developed the bilayer tablet having lag time of 4 hours, that is tablet is taken and bed time and drug releases take place a lag time of 4 hours when chances of gout are more.

LITERATURE SURVEY:

Goke *et al* (2019) studied that low aqueous solubility of active pharmaceutical ingredient present a serious challenge in development of new drug product. Challenges related to solubility have been enhanced over time and thus it is more prominent with a newly discovered substance than for the established substances. [11]

Devis *et al* (2017) significant and major issue in the pharmaceutical industry is poorly water soluble drug. Spray drying is excellent technique for fast removal of solvent from the system and yielding the particles of various properties. Spray drying technique has brought importance because of its efficacy and driving force for poorly relevant solvent. [12]

Lee Ram Ah *et al* (2017) formulated bilayer tablet of telmisartan and amlodipine byleaste using quality by design (QbD) approach. Based on the basic or primary knowledge response and targeted value of the group control factor was designed. The quantitative response of different factors was determined by using the best fit equation and linearity was seen between the predicted and actual value. [13]

Fu Xiang *et al* (2016) employing bilayer tablet manufacturing technology immediate release and extended release tablet was developed. Acceptable release uniformity was observed in this tablet. The release pattern was controlled by the diffusion process and by the erosion of HPC-S. In this study feasibility of developing immediate release and extended release formulation of tablet amoxicillin for once daily use using single bilayer tablet technology. [14]

Pujari S Prakash *et al* (2016) bilayer tablet of metformin and sitagliptin phosphate was prepared in combination for the treatment of type II diabeties mallitus. The relevance of preparing this was to reduce dose, dosing frequencies and associated side effects and to improve bioavailability which improve the patient compliance. It was found that combination of HPMC K 100 and sodium CMC gave appropriate sustained release for 12 hours. [15]

Momin *et al* (2015) bilayer tablet of venlafaxin hydrochloride for biomodel drug release was prepared. In this the bioadhesion study showed the increase amount of either polymer. Thus

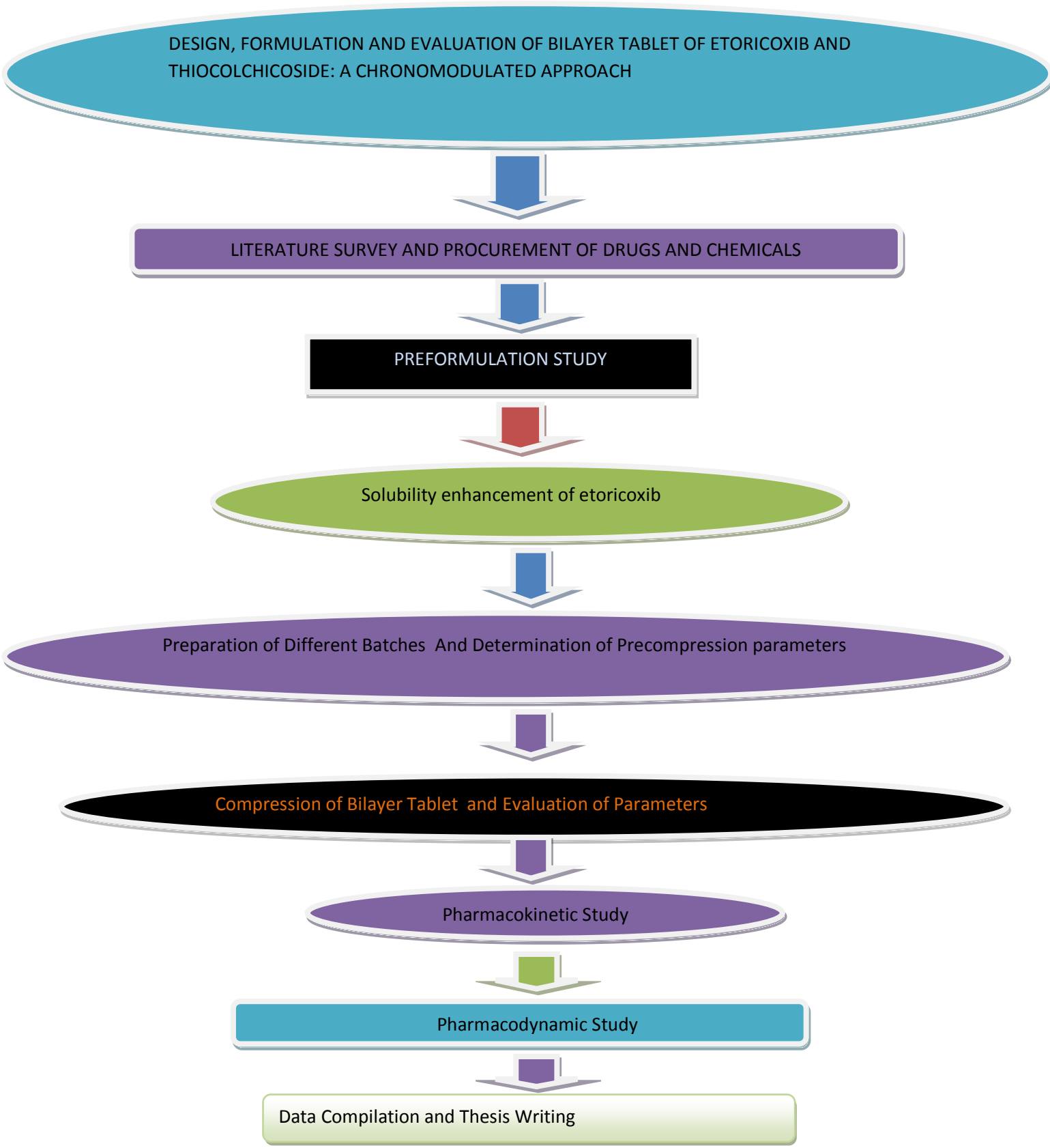
adhesive surface for maximum contact with mucin was increased and flexibility for interpenetration of mucin was increased. [16]

Vedhi *et al* (2015) study was carried out on 42 rats which were categorized into seven groups containing six rats in each group. At the end of study blood collection was carried out and was analysed for haematological and biochemical parameters. After collection of sample for 29 days rat were scarified and post mortem was carried out to study the various histopathological changes. [10]

Majeed M Saad *et al* (2014) bilayer tablet containing antimicrobial agent amoxicillin and antisecratory agent esomeprazole was prepared by applying the concept of bilayer tablet system for treatment of *H.Pylori* associated gastric ulcer. In this amoxicillin was prepared as sustained release tablet by using polymers in different ratios. [17]

Sayed Sultana Meraj *et al* (2013) Bilayer tablet generally provide relevant design approaches with incompatible drugs with different indications and same drugs with different release profile can be incorporated in single unit. Bilayer tablet is proved as more relevant technology as compared to single layer tablet. It is considered as important for sequential release of two drugs in combination. [18]

PROPOSED RESEARCH METHODOLOGY:


DESIGN, FORMULATION AND EVALUATION OF BILAYER TABLET OF ETORICOXIB AND THIOCOLCHICOSIDE: A CHRONOMODULATED APPROACH
LITERATURE SURVEY AND PROCUREMENT OF DRUGS AND CHEMICALS
PREFORMULATION STUDY
Solubility enhancement of etoricoxib
Preparation of Different Batches And Determination of Precompression parameters
Compression of Bilayer Tablet and Evaluation of Parameters
Pharmacokinetic Study
Pharmacodynamic Study
Data Compilation and Thesis Writing

Plan of Work

Phase	**Plan of work**
Phase 1	1. Literature Survey 2. Procurement of drugs and chemicals
Phase 2	Preformulation study of drug and excipients
Phase 3	Solubility enhancement of drug etoricoxib by different methods and comparision of solubility
Phase 4	Optimization of Formulation by QbD Softwares, Formulation bilayer tablet
Phase 5	Tablet Coating, evaluation of Bilayer Tablet and Pharmacokinetic studies
Phase 6	Pharmacodynamic studies
Phase 7	Accelerated Stability Study
Phase 8	Data Compilation and Thesis Writing

Equipments Commonly Used:

S.No	Name of Equipment	Company
1	Electronic Weighing Balance	Shimadzu Co. Ltd
2	FTIR Spectrophotometer	Shimadzu Co. Ltd. Japan
3	Ultraviolet Double Beam Spectrophotometer	Shimadzu Co. Ltd. Japan
4	Tablet Punching Machine	Trover Pharma Mach Jalandhar
5	Friability Test Apparatus	Roche
6	Disintegration Test Apparatus	LAB INDIA, Maharashtra, India
7	8- Station Dissolution Test Apparatus	LAB INDIA, Maharashtra, India
8.	Sieves	Bhushan Engineering and Scientific Traders Ambala
9.	pH Meter	Lab India
10.	Hot Air Oven	Navyug
11.	Vernier Caliper	Aerospace

Chemicals Required:

S.No	Chemical Requied	Category	Manufacturer/Supplier
1.	Etoricoxib	API	Prudence Pharma Chem. Gujrat
2.	Thiocolchicoside	API	Ryze Lifecare, Puchcula
3.	Polyvinyl Pyrollidone	Binder	B B Chemicals, Aurangabad
4.	Methanol	Solvent	LOBA Chemie Pvt.Ltd. Mumbai
5.	Cyclodextrin	Complexing Agent	Rubicon Pharmaceutical Aurangabad
6.	Crospovidone	Superdisintegrant	Ambika Drugs and Chemicals Pontasahib
7.	Croscarmellose Sodium	Superdisintegrant	Akhil Health Care Pvt. Ltd. Vadodra
8.	Sodium Starch Glycolate	Superdisintgrant	B B Chemicals Aurangabad
9.	Eudragit S100	Polymer	Central Drug House (P) Ltd., New Delhi
10.	Magnesium Stearate	Lubricant	Qualikems
11.	Lactose	Diluent	Himedia
12.	Starch	Binder	LOBA Chemie Pvt.Ltd. Mumbai

TENTATIVE CHAPTER PLAN:

S.No	Name of Chapter
1	Introduction
2	Literature Survey
3.	Research Envisaged
4.	Experimental
5.	Results and Discussion
6.	Summary and Conclusion

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Signature of Candidate Signature of Co-Guide Signature of Guide